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BROMOAMIDES AS STARTING MATERIALS IN THE SYNTHESIS OF α -HYDROXY- AND α -ALKOXY DERIVATIVES

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Abstract:Silver oxide promotes substitution of the
bromine at position 2 of α -
bromocarboxamides, with a hydroxyl or an
alkoxyl group.

 α -Hydroxy- and α -alkoxyderivatives of amides are important compounds as intermediates in organic synthesis and/or as biologically active derivatives in pharmaceutical chemistry.

While a variety of methods are disposable for the production of α -hydroxy carbonyl compounds ¹, literature is not so rich in studies on the α -hydroxylation neither of carboxylic acids 2,3,4,5, nor of esters 6,7,8 and amides. α -Hydroxylation of amides is moreover limited to N,N-dialkyl ones ^{9,3} except few particular cases.

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We wish to report here our method that proceeds via substitution of the bromine at the alfa carbon of the pertinent α -bromocarboxamide by both the hydroxyl and the alkoxyl groups: the formation of the ether linkage is achieved using silver oxide as condensing agent.



 α -Hydroxyderivatives of α -bromoisobutyramides, as prototype of starting materials hindered at C alfa, (Scheme 1) are obtained as pure products, in good yields, stirring reactions at room temperature from 90 min to 12 hours.

Scheme 1

bromoamide	R' = R" =CH ₃	hydroxy derivative
R' Br O	$\mathbf{R}^{\prime\prime\prime} = \mathbf{C}\mathbf{H}_2 \mathbf{-} \mathbf{C}_6 \mathbf{H}_5$	90% ; 12 h
	$R^{""} = C_6 H_5$	89% ;1.5 h
	$R''' = C(CH_3)_3$	86% ;1.5 h
	R''' = CH ₃	75%; 3 h

A preliminary study on hydroxylation of α bromopropionamides (e.g. N-benzyl- and N-terbutilamides) seems to evidence the same trend, but reaction time is longer while yields are good.

To shed light on further possibilities of the method, we synthesized some α -alkoxyderivatives of α -bromo-N-benzylisobutyramide (Scheme 2) and we found that two side products were present, determined as the pertinent hydroxy and elimination derivatives. While strictly anhydrous conditions hydroxyderivative formation, dehydrobromination avoid can product is always present whose amount depending on steric hindrance and nucleophilicity of the substituting alcohol and nature of NH moiety. Preliminary investigations showed that this side product indeed seems not present in other cycloalkanamides alkoxyamides derivatives, i.e. or propionamides.

This method cannot be useful when aprotic amides are employed ¹⁰.

Scheme 2

Pattern of reaction of α -bromo-N-benzyl-isobutyrlamide with various alcohols in the presence of Ag₂O

partner	alkoxy derivative	hydroxy derivative	elimination derivative
C ₂ H ₅ -OH	70% ; 66 h	10%	10%
(CH ₃) ₃ -C-OH	56% ; 3 days	12%	12%
C ₆ H ₅ -OH	50% ; 3 days	13%	13%

Reaction times become longer and yields lower as the steric hindrance of nucleophil increases. In the case of 2-adamanthol no reaction products were observed also refluxing 5 hours.

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We can therefore conclude that (1) hydroxylation yields of all the tested bromoamides were satisfactory; (2) in the case of alkoxylations (a) the reaction yields depend upon the steric hindrance of the alcohol and (b) presence and amount of side products depend upon the primary, secondary or tertiary nature of C alfa carbon and the nature of NH moiety.

Typical procedure:

2-bromo-N-benzyl-isobutyramide (512 mg, 2 mmol) dissolved in moist CH₃CN (5 ml) in the presence of silver oxide (232 mg, 1 mmol) was stirred overnight at room temperature. The reaction mixture was purified by passing the solution on a column filled by neutral alumina covered with a layer of Celite 577. Evaporation to dryness gave an oil (350 mg, 90.5%, Rf.0.25 in ethyl acetate-toluene 1:4) that cristallyzed by treatment with ethyl ether (colorless solid, pf.133-35°C). ¹H-NMR (CDCl₃): δ 1.40 (s, 6H, 2CH₃); 4.35 (d, 2H, CH₂, J=5.22Hz); 7.35 (s, 5H, C₆H₅). Elem. anal., found % (calcd. for C₁₁H₁₅NO₂): C, 68.42 (68.37); H, 7.88 (7.82); N, 7.35 (7.24).

If α -alkoxyderivatives are prepared, distilled CH₃CN must be used beside the proper alcohols.

<u>References</u> :

- 1
- Gore, M.P. and Vederas J.C., <u>J.Org.Chem.</u>, 1986, 3700 and citations therein.

α-HYDROXY- AND α-ALKOXY DERIVATIVES

2	Kobayashi, T.; Sakakura, T. and Tanaka, M.,
	<u>Tetrahedron Lett.</u> , <u>1987</u> , 2721.
3	Pohmakotr, M. and Winotai, C., Synthetic Comm.,
	<u>1988,</u> 2141.
4	Iwasaki, G.; Kimura, R., Numao, N. and Kondo, K.;
	<u>Chem.Pharm.Bull.</u> , <u>1989</u> , 280.
5	Shimizu, I.; Tekawa, M.; Maruyama, Y. and
	Yamamoto, A., <u>Chemistry Lett.</u> , <u>1992</u> , 1365.
6	El-Abadelah, M.M., <u>Tetrahedron, 1973</u> , 589.
7	Vedejis, E.; Engler, D.A. and Telschow, J.E.,
	J.Org.Chem., 1978, 188.
8	Davis, F.A.; Vishwakarma, L.C.; Billmer, J.M. and
	Finn, J., <u>J.Org.Chem., 1984</u> , 3243.
9	Wassermann, H.H. and Lipshutz, B.H., Tetrahedron
	Lett., <u>1975</u> , 1731.
10	Cavicchioni, G.; D'Angeli, F.; Casolari, A. and
	Orlandini P., <u>Synthesis</u> , <u>1988</u> , 947.

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